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(54) Biocidal composition and use

(57) A composition comprises an isothiazolinone or an isothiazolothione derivative and a disulphide compound in which at least one of the groups attached to the disulphide contains a nitrogen-oxide structure, a group R_2NCX or a group $CXOR^1$, where R is hydrogen or a hydrocarbyl group at least one R being a hydrocarbyl group, R^1 is hydrogen or hydrocarbyl and X is an oxygen or sulphur atom. The isothiazolinone derivative can be 1,2-benzisothiazolin-3-one. The disulphide can be 2,2'-dithio-pyridine-1,1'-dioxide; tetramethyldithiocarbamate-disulphide; 2,3-dichloro-3-phenyldithio-N-methylacrylamide or 3,3'-thiodipropionic acid. Compositions of this type show antimicrobial properties and are effective against a range of bacteria and fungi.

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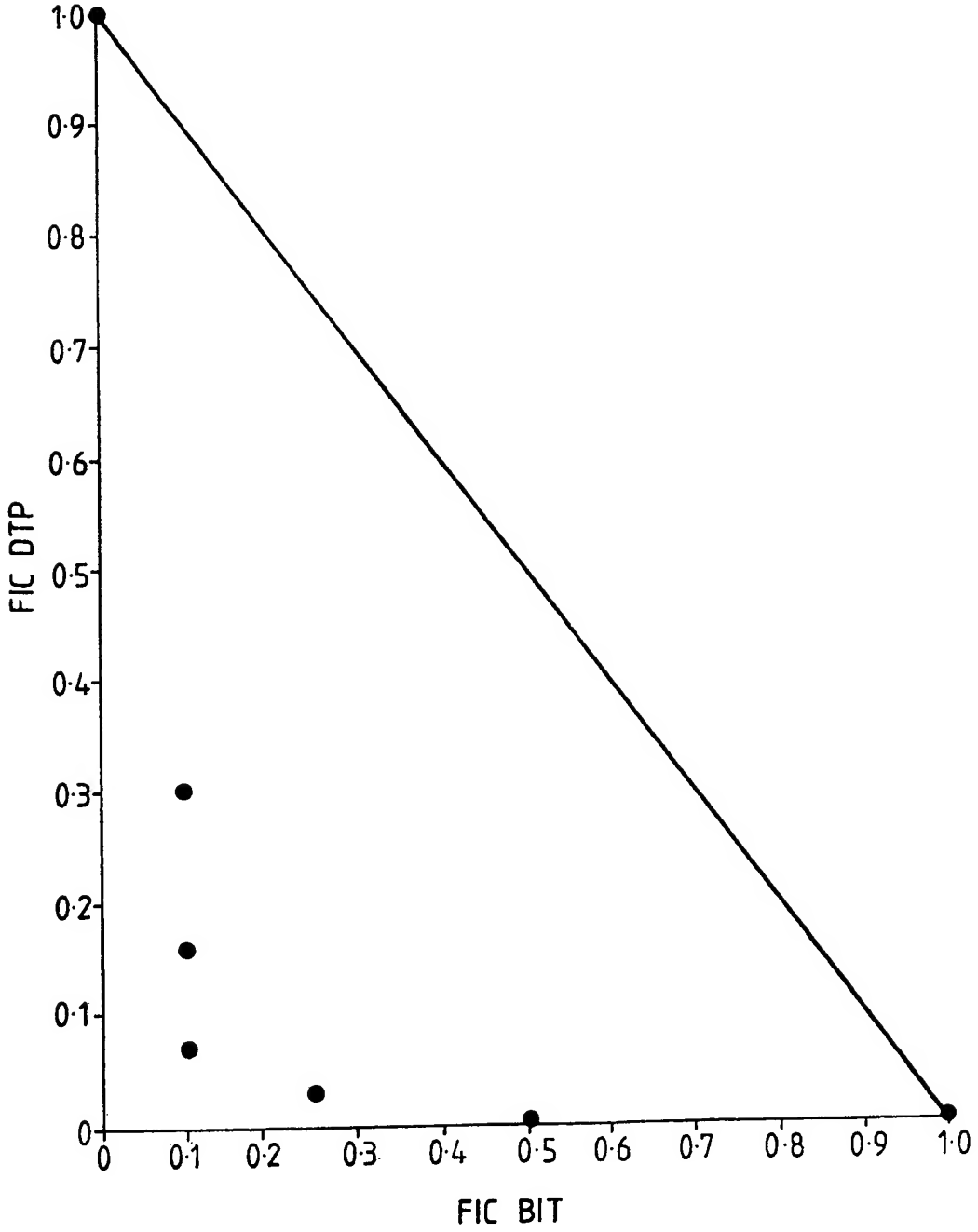
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COMPOSITION AND USE

The present invention relates to compositions which are useful as industrial biocides.

Industrial biocides are useful to prevent industrial spoilage, in particular that caused by bacteria and fungi. Industrial biocides find application in the preservation of paints, latices, adhesives, leather, wood, metal working fluids and cooling water.

One class of compound which can be used as an industrial biocide is based on the isothiazolinone structure. There are many disclosures of isothiazolinone derivatives which are stated to have useful biocidal properties. US Patent 3761488 discloses isothiazolinone derivatives in which alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl or aryl groups, which may optionally be substituted, are attached to the nitrogen atom and the 4 and 5 positions are unsubstituted or are substituted with halogen or lower alkyl groups. US Patent 3517022 discloses benzisothiazolones in which a carbamoyl group is attached to the nitrogen atom and the benzene ring may be optionally substituted. US Patent 3950349 discloses N-thio-substituted isothiazolin-3-one compounds which may be isothiazolone or benzisothiazolone derivatives. US Patent 4165318 discloses a solution of a 3-isothiazolone in a polar organic solvent, wherein the solution also contains a stabilising amount of formaldehyde. British Patent Specification 2087388 discloses 4,5-polymethylene-4-isothiazoline-3-one in which the polymethylene chain has three or four carbon atoms.

Another class of compound which is stated to be fungicidal is based on the isothiazolothione structure. British Patent Specification 1113634 discloses compounds of this type or an isomeric form thereof, in which the 4 and 5 positions are unsubstituted or may be substituted with alkyl or aryl groups or which may form a part of a further ring system.

Compounds of the foregoing types, and related compounds of the same general type, are effective to a varying degree, depending on the particular compound, against a range of bacteria and/or fungi. However, to reduce the cost of using these compounds it is desirable to improve their effectiveness as antimicrobial materials.

Compositions have been proposed which contain more than one compound which has antimicrobial properties. In general such compositions show an aggregate of the properties of the compounds present in the composition. Typically such compositions contain one compound which exhibits useful antibacterial properties together with a different compound which exhibits useful antifungal properties.

We have now found that certain compositions possess surprisingly useful antimicrobial properties.

Thus, according to the present invention there is provided a composition which comprises

(a) at least one isothiazolinone derivative or at least one isothiazolothione derivative, and

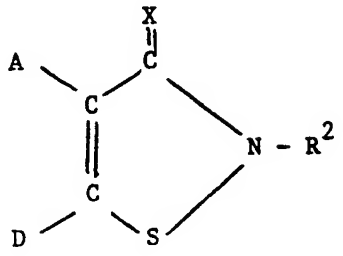
(b) at least one disulphide compound in which at least one of the groups attached to the disulphide contains a nitrogen-oxide structure, a group $(R)_2NCX-$ or a group $-CXOR^1$, wherein

each R is, independently, a hydrogen atom or a hydrocarbyl group, at least one of the groups R being a hydrocarbyl group;

R^1 is a hydrogen atom or a hydrocarbyl group; and

X is an oxygen or sulphur atom.

The isothiazolinone or isothiazolothione derivative which is component (a) of the composition is typically a compound of the general formula:



wherein:

X is as hereinbefore defined;

R^2 is a hydrogen atom, a substituted or unsubstituted hydrocarbyl group, a substituted or unsubstituted hydrocarbylthio group, a substituted or unsubstituted hydrocarbyloxy group, or a carbamoyl group;

A is a hydrogen atom, a halogen atom, a cyano group, or a substituted or unsubstituted hydrocarbyl group;

D is a hydrogen atom, a halogen atom, a cyano group, or a substituted or unsubstituted hydrocarbyl group; or

A and D, together with the carbon atoms to which they are attached, form a five- or six-membered ring, which may optionally be substituted.

Preferably component (a) is at least one isothiazolinone derivative, that is a compound in which X is an oxygen atom. If the groups R^2, A and D are, or contain, substituted hydrocarbyl groups, the substituents are typically halogen, alkoxy or alkylthio, particularly those in which the alkyl groups contain 1 to 4 carbon atoms. If R^2 is a carbamoyl group, this is of the general type $-CONHR^3$ where R^3 is a hydrogen atom or a hydrocarbyl group, which may be substituted. It is generally preferred that the group R^2 is a hydrogen atom or a lower alkyl group, that is an alkyl group containing 1 to 4 carbon atoms. R^2 is especially hydrogen or a methyl group.

A and D may, together with the carbon atoms to which they are attached, form a five- or six-membered ring, which may be substituted, the substituents typically being halogen, alkyl, alkoxy or alkylthio groups. The ring thus obtained may contain a heteroatom, for example a nitrogen atom but in general A and D form a hydrocarbon ring such as a benzene, cyclopentene or cyclohexene ring. Alternatively, A and D are separate groups and one or both of A and D can be a hydrogen atom. It is generally preferred that at least one of A and D is other than a hydrogen atom and is, particularly, a halogen atom, for example chlorine or a lower alkyl group.

Compounds which can be used as component (a) of the mixture include 5-chloro-2-methylisothiazolin-3-one (R^2 is methyl, A is hydrogen and D is chlorine); 4,5-dichloro-2-methylisothiazolin-3-one (R^2 is methyl and A and D are both chlorine); 1,2-benzisothiazolin-3-one (R^2 is hydrogen and A and D, together with the carbon atoms to which they are attached, form a benzene ring); 4,5-trimethylene-4-isothiazolin-3-one (R^2 is hydrogen and A and D, together with the carbon atoms to which they are attached, form a cyclopentene ring); and 2-methyl-4,5-trimethylene-4-isothiazolin-3-one (R^2 is methyl and A and D, together with the carbon atoms to which they are attached, form a cyclopentene ring).

Component (b) of the composition is a disulphide compound and is typically of the general formula:

$$R^4 - S - S - R^5$$

wherein:

R^4 is a group which contains a nitrogen-oxide structure, a group $(R)_2NCX-$ or a group $-CXOR^1$;

R^5 is a hydrogen atom, a substituted or unsubstituted hydrocarbyl group, or a group which contains a nitrogen-oxide structure, a group $(R)_2NCX-$ or a group $-CXOR^1$; and

R, R^1 and X are all as hereinbefore defined.

The groups R^4 and R^5 may be the same or different. R^5 may be a hydrogen atom or a substituted or unsubstituted hydrocarbyl group and if R^5 is selected from these groups it is preferred that R^5 is a substituted or unsubstituted aryl group, for example a phenyl group.

It is generally preferred that R^4 and R^5 both are groups which contain a nitrogen-oxide structure, a group $(R)_2NCX-$ or a group $-CXOR^1$. R^4 and R^5 may be different groups of the foregoing type but it is generally preferred that R^4 and R^5 are the same. The nitrogen-oxide structure group, $(R)_2NCX-$ or group $-CXOR^1$ may be attached directly to the disulphide group or may be attached through a linking group which is typically a hydrocarbyl or substituted hydrocarbyl group.

The nitrogen-oxide structure is typically present as a pyridine oxide group. The group $(R)_2NCX-$ is preferably one in which both of the groups R are hydrocarbyl groups, especially alkyl groups such as lower alkyl groups. Conveniently the groups R are both the same, for example both are methyl groups. The group $-CXOR^1$ may be one in which R^1 is an alkyl group, for example an alkyl group containing up to 20 carbon atoms. However, it is convenient to use a group $-CXOR^1$ in which X is oxygen and R^1 is hydrogen.

Compounds which can be used as component (b) in the compositions of the present invention include 2,2'-dithiopyridine-1,1-dioxide; N,N,N',N'-tetramethyldithiocarbamate disulphide; 2,3-dichloro-3-phenyldithio-N-methylacrylamide; and 3,3'-dithiopropionic acid.

We have obtained particularly useful compositions using 1,2-benzisothiazolin-3-one together with either 2,2'-dithiopyridine-1,1'-dioxide or N,N,N',N'-tetramethyldithiocarbamate disulphide.

The relative proportions of the components of the composition can vary and compositions having useful properties can be obtained which contain 1% by weight of component (a) or component (b) and correspondingly 99% by weight of component (b) or component (a).

The preferred proportions are dependent on the compounds used as component (a) and component (b), and also the particular system in which the mixture is to be used. In general the composition contains at least 2% by weight of each component and especially at least 8% by weight of each component.

The compositions of the present invention have antimicrobial properties. We have found that compositions in accordance with the present invention are active against both bacteria and fungi. Furthermore, compositions in accordance with the present invention are such that the sum of the fractional inhibitory concentration (FIC) for all the components of the composition is less than one and, specifically, is less than 0.7. Preferred compositions are those in which the sum of the FIC for all the components of the composition is not more than 0.5. The FIC is the ratio of the concentration of an individual component to the minimum inhibitory concentration of that component. It will be appreciated that if the value of the sum of the FIC for all the components of the composition is less than one, the composition is synergistic, the extent of synergy being indicated by the amount by which the sum of the FIC is below one. We have found that some compositions in accordance with the present invention are such that the sum of the FIC is as low as 0.3 or even 0.2 and may be even lower.

The compositions of the present invention have antimicrobial properties and are suitable for use as industrial biocides.

The compositions of the present invention provide good wet state preservation and hence may be used as a cutting fluid preservative and also in cooling water applications. Wood and leather preservation is another field of application of the compositions. The compositions of the present invention can also be incorporated into paint, as paint film fungicide that can be used without addition of a bactericide.

The compounds which are component (a) and component (b) of the composition of the present invention are soluble in many polar solvents, although the solubility is dependent on the nature of the

particular compounds which are present in the composition. However, many of the compounds are soluble in water, alcohols, ethers, ketones and other polar solvents or mixtures thereof.

The compositions of the present invention may consist only of component (a) and component (b). However, typically the composition comprises component (a) and component (b) as a solution, suspension or emulsion in a suitable liquid medium such as water. The composition may comprise a suspension or emulsion of component (a) and component (b), or a solution of one or both of components (a) and (b), in a liquid medium in which at least one of components (a) and (b) is insoluble.

The composition may be incorporated into the medium to be protected using any suitable mixing technique. The composition is incorporated into the medium to be protected in an amount to provide from 0.0001 to 5% by weight of the composition relative to the medium in which it is incorporated. If the composition is being used to preserve a solid substrate such as leather or wood, the composition may be applied directly to the substrate or may be incorporated into a coating composition such as a paint, varnish or lacquer which is then applied to the substrate. Alternatively, the solid material may be impregnated with the composition of the present invention.

The composition of the present invention can be used for the treatment of various media to inhibit the growth of micro-organisms.

Thus, as a further aspect of the present invention there is provided a method for inhibiting the growth of micro-organisms on, or in, a medium which comprises treating the medium with a composition of components (a) and (b) as hereinbefore defined.

The composition can be used in conditions in which micro-organisms grow and cause problems such as, for example, in aqueous environments including cooling water systems, paper mill liquors, metal working fluids, geological drilling lubricants, polymer emulsions, and emulsion paints. The composition can also be used to impregnate solid materials such as wood or leather or can be coated onto the surfaces thereof directly or incorporated into a paint, varnish or lacquer.

Further aspects of the present invention are described in the following illustrative examples.

In the following examples, compositions in accordance with the present invention were subjected to evaluation of the antimicrobial properties of the compositions. The evaluation was effected, under sterile conditions throughout, as follows:

In the microbiological evaluation, various compositions were tested for anti-microbial activity against bacteria and/or fungi. The bacteria used were one or more of Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa. The fungi used were one or more of Aspergillus niger, Aureobasidum pullulans, Cladosporium sphaerospermum, Aspergillus versicolor, and Chaetomium globosum.

These test organisms will be referred to hereafter as EC, SA, PA, AN, AP, CS, AV and CG respectively.

Microbiological evaluation

Method A

The materials, or mixture of materials, to be tested were added to a nutrient broth in amounts to give a desired concentration of the added material. The added materials were added at concentrations from zero to above the minimum inhibitory concentration of the particular material In the mixtures, the concentrations of each material were varied in a systematic fashion to give a matrix of mixtures of different relative proportions and different total concentrations.

The effect on the inhibition of growth of bacteria was investigated by inoculating each sample of broth with sufficient of the test bacterium to give about 10^5 cells cm^{-3}. The mixture was incubated at 30°C for 48 hours. At the end of the test period the presence of turbidity in the broth indicated that growth of the test bacterium had occurred. A lack of turbidity was indicative that no growth had occurred. The results were used to draw an isobologram from which the sum of the fractional inhibitory concentration for a mixture can be determined.

Method B

The material, or mixture of materials, to be tested was dissolved in a suitable solvent. The solution obtained was diluted with a further quantity of the same solvent to give product solution with desired concentrations of the added material or materials.

To a suitable agar medium was added a quantity of one of the product solutions to give the required amount of the added material or materials in the agar. The resulting agar medium was poured into petri dish plates and allowed to set.

The test organisms were surface inoculated onto the test plates by means of a multi-point inoculator. Each test plate was inoculated with all of the test fungi. The plates were incubated for four days at 25°C.

At the end of the incubation period, the plates were assessed visually for growth of the micro-organisms. The amount of each material which inhibited the growth of a particular fungus was recorded together with all the mixtures which inhibited growth of the same fungus. From this data the sum of the fractional inhibitory concentration of each mixture could be determined.

Example 1

The microbiological evaluation as described in Method A was carried out using the bacterium, Escherichia coli. The composition tested was a mixture of 1,2-benzisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide.

The concentrations of 1,2-benzisothiazolin-3-one used were 0, 1, 2.5, 5 and 10 microgram cm^{-3}. 2,2'-dithiopyridine-1,1'-dioxide was used at concentrations of 0, 0.1, 0.5, 1, 2.5, 5 and 10 microgram cm^{-3}.

An isobologram was drawn from the data obtained and this is as in the accompanying Figure in which BIT represents 1,2-benzisothiazolin-3-one and DTP represents 2,2'-dithiopyridine-1,1'-dioxide. The lowest sum of the fractional inhibitory concentration (FIC) was 0.2 which was achieved with a mixture containing 1 microgram cm^{-3} of 1,2-benzisothiazolin-3-one and 1 microgram cm^{-3} of 2,2'-dithiopyridine-1,1'-dioxide.

Example 2

The procedure of Example 1 was repeated using different concentrations of 1,2-benzisothiazolin-3-one and replacing 2,2'-dithiopyridine-1,1'-dioxide by N,N,N',N'-tetramethyldithiocarbamate disulphide.

The concentrations of 1,2-benzisothiazolin-3-one used were 0, 1, 2.5, 5, 7.5 and 10 microgram cm^{-3}. N,N,N'.N'-tetramethyldithiocarbamate disulphide was used at concentrations of 0, 10, 25, 50, 75 and 110 microgram cm^{-3}.

No growth of the bacterium was observed in any of the mixtures (including 1 microgram cm^{-3} of 1,2-benzisothiazolin-3-one and 10 microgram cm^{-3} of N,N,N',N'-tetramethyldithiocarbamate disulphide).

From this it was concluded that the lowest sum of the fractional inhibitory concentration was less than 0.2 which was achieved with a mixture containing 1 microgram cm^{-3} of 1,2-benzisothiazolin-3-one and 10 micrograms cm^{-3} of N,N,N',N'-tetramethyldithiocarbamate disulphide.

Example 3

The procedure of Example 1 was repeated using different concentrations of 1,2-benzisothiazolin-3-one and replacing 2,2'-dithiopyridine-1,1'-dioxide by 2,3-dichloro-3-phenyldithio-N-methacrylamide.

The concentrations of 1,2-benzisothiazolin-3-one used were 0, 1, 2, 4, 6, 8 and 10 microgram cm^{-3}. 2,3-dichloro-3-phenyldithio-N-methylacrylamide was used at concentrations of 0, 1, 2, 4, 6, 8, 10 and 15 microgram cm^{-3}.

The lowest sum of the fractional inhibitory concentration was less than 0.4 which was achieved with a mixture containing 2 micrograms cm^{-3} of 1,2-benzisothiazol-3-one and 1 microgram cm^{-3} of 2,3-dichloro-3-phenyldithio-N-methylacrylamide.

Example 4

The procedure of Example 1 was repeated using the bacterium Pseudomonas aeruginosa, different concentrations of 1,2-benziso-thiazolin-3-one and replacing 2,2'-dithiopyridine-1,1'-dioxide by 3,3'-dithiodipropionic acid.

The concentrations of 1,2-benzisothiazolin-3-one used were 0, 1, 5, 10, 20 and 30 microgram cm^{-3}. 3,3'-dithiopropionic acid was used at concentrations of 0, 50, 100, 200, 250, 300, 350, 400 and 540 microgram cm^{-3}.

The lowest sum of the fractional inhibitory concentration was less than 0.4, which was achieved with a mixture containing 5 micrograms cm^{-3} of 1,2-benzisothiazolin-3-one and 100 micrograms cm^{-3} of 3,3'-dithiopropionic acid.

Example 5

The microbiological evaluation as described in Method B was carried out using 1,2-benzisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide.

The concentrations of 1,2-benzisothiazolin-3-one used were 0, 1, 5, 10, 15, 20 and 70 microgram cm^{-3}. 2,2'-dithiopyridine-1,1'-dioxide was used at concentrations of 0, 0.5, 1, 5, 10, 20 and 40 microgram cm^{-3}.

The results obtained with the fungi under test depended on the particular fungus.

Using the fungi AP and AV, there was no detectable growth of these fungi under the evaluation conditions in the presence of both agents at all concentrations including 1 microgram cm^{-3} of 1,2-benzisothiazolin-3-one with 0.5 microgram cm^{-3} of 2,2'-dithio-pyridine-1,1'-dioxide.

Using the fungus AN, the sum of fractional inhibitory concentration exhibited a minimum of 0.3 for the following mixtures as set out in Table 1.

Table 1

BIT (a) (b)	DTP (a) (c)
1	20
5	10
10	1

Notes to Table 1

(a) Quantities are given as microgram cm^{-3}

(b) BIT is 1,2-benzisothiazolin-3-one

(c) DTP is 2,2'-dithiopyridine-1,1'-dioxide.

Using the fungus CG, the sum of fractional inhibitory concentration exhibited a minimum of 0.3 for a mixture of 1 microgram cm^{-3} of 1,2-benzisothiazolin-3-one and 1 microgram cm^{-3} of 2,2'-dithiopyridine-1,1'-dioxide.

Using the fungus CS, the sum of fractional inhibitory concentration exhibited a minimum of 0.2 for a mixture of 1 microgram cm^{-3} of 1,2-benzisothiazolin-3-one and 5 microgram cm^{-3} of 2,2'-dithiopyridine-1,1'-dioxide.

Example 6

To samples of a metal working fluid were added various materials and a mixture of materials. The quantity of added materials was sufficient to give concentrations of total added material of 0.125% w/v, 0.25% w/v and 0.5% w/v. The oil mixtures were then mixed with sterilised, deionised water in the proportion, by volume, of 1:19 oil mixture to water.

To 50 cm^3 of the oil-water mixture obtained as described was added, at intervals, a cell suspension of the bacterium Pseudomonas aeruginosa (PA). A sample of the mixture was taken for a cell count at intervals.

The results at the end of a three week period are summarised in Table 2.

Table 2

Additive (b) (d)	Conc. (e)	Cell Count (f)
BIT	0.125	3.7×10^6
BIT	0.25	7.8×10^6
BIT	0.5	NIL
TDS	0.125	3×10^7
TDS	0.25	1.2×10^7
TDS	0.5	3×10^7
BIT/TDS (9:1)	0.125	6.9×10^5
BIT/TDS (9:1)	0.25	NIL
BIT/TDS (9:1)	0.5	NIL

Notes to Table 2

(b) is as defined in Notes to Table 1.

(d) TDS is N,N,N',N'-tetramethyldithiocarbamate disulphide; 9:1 is the relative proportions by weight of the mixture.

(e) Concentration is the % w/v of the additive, or mixture of additives, relative to the mineral oil.

(f) The cell count was determined using the procedure described by A.L.Koch on pages 185-187 of "Manual of Methods for General Bacteriology" published by the American Society for Microbiology.

Example 7

The procedure of Example 1 was repeated using 5-chloro-2-methylisothiazolin-3-one rather than 1,2-benzisothiazolin-3-one and using different concentrations of 2,2'-dithiopyridine-1,1'-dioxide.

The concentrations of 5-chloro-2-methylisothiazolin-3-one used were 0, 0.05, 0.1, 0.25, 0.5 and 1 microgram cm^{-3}. 2,2'-dithiopyridine-1,1'-dioxide was used at concentrations of 0, 1, 2.5, 5, 7.5 and 15 microgram cm^{-3}.

The lowest sum of the fractional inhibitory concentration was less than 0.4 which was achieved with a mixture containing 0.1 microgram cm^{-3} of 5-chloro-2-methylisothiazolin-3-one and 1 microgram cm^{-3} of 2,2'-dithiopyridine-1,1'-dioxide.

Example 8

The procedure of Example 1 was repeated using 4,5-dichloro-2-methylisothiazolin-3-one rather than 1,2-benzisothiazolin-3-one and using different concentrations of 2,2'-dithiopyridine-1,1'-dioxide.

The concentrations of 4,5-dichloro-2-methylisothiazolin-3-one used were 0, 0.05, 0.1, 0.25, 0.5 and 1 microgram cm^{-3}. 2,2'-dithiopyridine-1,1'-dioxide was used at concentrations of 0, 1, 2.5, 5, 7.5 and 15 microgram cm^{-3}.

The lowest sum of the fractional inhibitory concentration was less than 0.4 which was achieved with a mixture containing 0.05 microgram cm^{-3} of 4,5-dichloro-2-methylisothiazolin-3-one and 2.5 microgram cm^{-3} of 2,2'-dithiopyridine-1,1'-dioxide.

CLAIMS

1. A composition which comprises

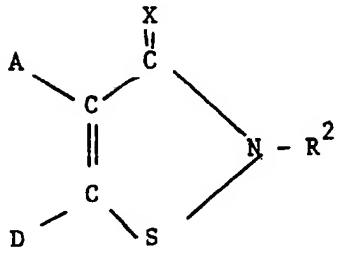
(a) at least one isothiazolinone derivative or at least one isothiazolothione derivative, and

(b) at least one disulphide compound in which at least one of the groups attached to the disulphide contains a nitrogen-oxide structure, a group $(R)_2NCX-$ or a group $-CXOR^1$, wherein each R is, independently, a hydrogen atom or a hydrocarbyl group, at least one of the groups R being a hydrocarbyl group;

R^1 is a hydrogen atom or a hydrocarbyl group; and

X is an oxygen or sulphur atom.

2. A composition as claimed in claim 1 wherein (a) is at least one compound of the general formula:



wherein:

X is as hereinbefore defined;

R^2 is a hydrogen atom, a substituted or unsubstituted hydrocarbyl group, a substituted or unsubstituted hydrocarbylthio group, a substituted or unsubstituted hydrocarbyloxy group, or a carbamoyl group;

A is a hydrogen atom, a halogen atom, a cyano group, or a substituted or unsubstituted hydrocarbyl group;

D is a hydrogen atom, a halogen atom, a cyano group, or a substituted or unsubstituted hydrocarbyl group; or

A and D, together with the carbon atoms to which they are attached, form a five- or six-membered ring, which may be substituted.

3. A composition as claimed in claim 2 wherein in component (a) X is an oxygen atom.

4. A composition as claimed in either claim 2 or claim 3 wherein R^2 is a carbamoyl group of the type $-CONHR^3$, wherein R^3 is a hydrogen atom or a substituted or unsubstituted hydrocarbyl group.

5. A composition as claimed in either claim 2 or claim 3 wherein R^2 is a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms.

6. A composition as claimed in any one of claims 2 to 5 wherein A and D together with the carbon atoms to which they are attached, form a substituted or unsubstituted five- or six-membered hydrocarbon ring.

7. A composition as claimed in any one of claims 2 to 5 wherein one of the groups A and D is a halogen atom or an alkyl group containing 1 to 4 carbon atoms and the other of the groups A and D is a hydrogen atom, a halogen atom or an alkyl group containing 1 to 4 carbon atoms.

8. A composition as claimed in any one of claims 2, 3 and 5 to 7 in which component (a) is selected from 5-chloro-2-methylisothiazolin-3-one; 4,5-dichloro-2-methylisothiazolin-3-one; 1,2-benzisothiazolin-3-one; 4,5-trimethylene-4-isothiazolin-3-one and 2-methyl-4,5-trimethylene-4-isothiazolin-3-one.

9. A composition as claimed in any one of claims 1 to 8 wherein (b) is at least one compound of the general formula:

$$R^4 - S - S - R^5$$

wherein:
R^4 is a group which contains a nitrogen-oxide structure, a group $(R)_2NCX-$ or a group $-CXOR^1$;
R^5 is a hydrogen atom, a substituted or unsubstituted hydrocarbyl group, or a group which contains a nitrogen-oxide structure, a group $(R)_2NCX-$ or a group $-CXOR^1$; and
R, R^1 and X are all as hereinbefore defined.

10. A composition as claimed in claim 9 wherein R^5 is a substituted or unsubstituted aryl group.

11. A composition as claimed in claim 9 wherein R^4 and R^5 are both the same.

12. A composition as claimed in claim 11 wherein the nitrogen-oxide structure, the group $(R)_2NCX-$ or the group $-CXOR^1$ are attached to the disulphide group through a hydrocarbyl or substituted hydrocarbyl group.

13. A composition as claim in claim 9 wherein R^4 and R^5 are both pyridine oxide groups.

14. A composition as claimed in any one of claims 9, 11 and 12 wherein R^4 and R^5 both contain a group $(R)_2NCX-$ where both of the groups R are the same and are alkyl groups of 1 to 4 carbon atoms.

15. A composition as claimed in any one of claims 9, 11 and 12 wherein R^4 and R^5 both contain a group $-CXOR^1$ in which X is oxygen and R^1 is hydrogen.

16. A composition as claimed in claim 9 wherein component (b) is selected from 2,2'-dithiopyridine-1,1'-dioxide; N,N,N',N'-tetramethyldithiocarbamate disulphide; 2,3-dichloro-3-phenyldithio-N-methylacrylamide and 3,3'-dithiopropionic acid.

17. A composition as claimed in any one of claims 1 to 16 which contains from 1 to 99% by weight of (a) and correspondingly from 99 to 1% by weight of (b).

18. A composition as claimed in claim 17 which contains at least 2% by weight of (a) and of (b).

19. A composition as claimed in claim 18 which contains at least 8% by weight of (a) and of (b).

20. A composition as claimed in any one of claims 1 to 19 wherein the sum of the fractional inhibitory concentration of the components is less than 0.7.

21. A composition as claimed in claim 20 wherein the sum of the fractional inhibitory concentration of the components is not more than 0.5.

22. A composition as claimed in any one of claims 1 to 21 which comprises (a) and (b) as a solution, suspension or emulsion in a liquid medium.

23. A medium which is susceptible to attack by micro-organisms and which contains from 0.0001 to 5% by weight of the medium of a composition as claimed in any one of claims 1 to 21.

24. A medium as claimed in claim 23 which is selected from a cooling water system, a paper mill liquor, a metal working fluid, a geological drilling lubricant, a polymer emulsion, a paint, a lacquer or a varnish.

25. A method for inhibiting the growth of micro-organisms on, or in, a medium, which comprises treating the medium with a composition as claimed in any one of claims 1 to 22.

26. A method as claimed in claim 25 wherein the medium which is treated is a cooling water system, a paper mill liquor, a metal working fluid, a geological drilling lubricant, a polymer emulsion, a paint, a lacquer, a varnish, leather or wood.

27. A composition which contains 1,2-benzisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide wherein 1,2-benzisothiazolin-3-one is present in an amount of 1% to 99% by weight of the total weight of 1,2-benzisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide.

28. A composition which contains 1,2-benzisothiazolin-3-one and N,N,N',N'-tetramethyldithiocarbamate disulphide wherein 1,2-benzisothiazolin-3-one is present in an amount of 1% to 99% by weight of the total weight of 1,2-benzisothiazolin-3-one and N,N,N',N'-tetramethyldithiocarbamate disulphide.

29. A composition which contains 1,2-benzisothiazolin-3-one and 2,3-dichloro-3-phenyldithio-N-methacrylamide wherein 1,2-benziso-thiazolin-3-one is present in an amount of 1% to 99% by weight of the total weight of 1,2-benzisothiazolin-3-one and 2,3-dichloro-3-phenyldithio-N-methacrylamide.

30. A composition which contains 1,2-benzisothiazolin-3-one and 3,3'-dithiopropionic acid wherein 1,2-benzisothiazolin-3-one is present in an amount of 1% to 99% by weight of the total weight of 1,2-benzisothiazolin-3-one and 3,3'-dithiopropionic acid.

31. A composition which contains 5-chloro-2-methylisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide wherein 5-chloro-2-methylisothiazolin-3-one is present in an amount of 1% to 99% by weight of the total weight of 5-chloro-2-methylisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide.

32. A composition which contains 4,5-dichloro-2-methylisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide wherein 4,5-dichloro-2-methylisothiazolin-3-one is present in an amount of 1% to 99% by weight of the total weight of 4,5-dichloro-2-methylisothiazolin-3-one and 2,2'-dithiopyridine-1,1'-dioxide.

33. A composition as claimed in claim 1 and substantially as hereinbefore described with reference to the Examples.

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